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Evaluation of functional characteristics of lactose by inverse gas chromatography

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Abstract

The work was focused on the analysis of different batches of the common pharmaceutical excipient lactose using inverse gas chromatography (IGC). Several batches of amorphous (spray dried) and crystalline form of lactose were studied. Surface properties represented by the surface energy and specific (acid-base) interactions between probes and analyzed samples shows batch variations and significant differences between manufacturers and technological processes. The second part of this work was focused on effect of relative humidity and temperature on stability of lactose. The variations of surface energy and specific interactions over time were studied. The changes in surface properties of two batches of lactose- amorphous and crystalline caused by higher relative humidity were measured by IGC. From measured values are obvious different chemical and physical properties of both lactose forms. Negative effect of higher temperature and air humidity lead to changes in surface energy and mainly rapid changes of electron-acceptor and electron-donor surface sites. Lactose monohydrate shows dramatic decrease in the surface energy and in the strength of electron-accepting sites on the contrary of spray dried where the acidity of surface increased.

Keywords: Inverse gas chromatography; lactose monohydrate; spray dried lactose; increased humidity

1. Introduction

At the present, lactose is one of the most common excipients used in the pharmaceutical industry. It is particularly suitable in terms of minimum interaction with active ingredients and the other excipients,

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good availability and low costs. Over a long period lactose is primarily used in the pharmaceutical industry as excipient in the formulation of drugs, which is closely related to its relatively low sweetness, high stability, low hygroscopicity, low costs, good availability and safety and numerous applications in drug formulations. It covers a wide range of applications such as in the direct compaction, wet granulation and micronization to the devices of inhalational drugs [1].

Lactose exists in multiple forms, which have different properties, while some forms are more suitable for processing in certain formulations. A selection of the correct form of lactose in the formulation of drugs is very important. Mainly the reproducibility of the particle properties, which are required for the manufacture of consistent tablets, has to be kept [2].

There are several techniques and methods of lactose production, and there are significant differences between lactoses produced by different technological processes. E.g. spray drying forms amorphous lactose, by milling and sieving is formed crystalline one. Therefore, the prediction of long-term behaviour of lactose is very important characteristic of different types of lactose.

Lactose monohydrate is widely used as an excipient in processes where granulation and drying occur. It is often used for the production of the inhalational devices, which must be finely milled. Lactose acts here as a carrier of micronized drug and helps in transfer to the lungs. For direct compression an appropriate form of lactose appears to be α-lactose monohydrate containing a small amount of anhydrous lactose. It is used as the excipient in smaller quantities and dosage forms where granulation in the production is not required. Because α-lactose monohydrate is the cheapest form of lactose commercially available, it is also the most widely used.

Amorphous lactose prepared by spray drying technique has good flow and binding properties due to its high sphericity of agglomerates. Commonly it is combined with microcrystalline cellulose and is used as the excipient in the process of direct stamping [3].

A wide range of the methods for the analysis of lactose is known. In laboratory and also in the industrial scale are commonly used: differential scanning calorimetry, X-ray diffraction and IR spectroscopy. The method used in this work is the inverse gas chromatography (IGC). Application of IGC has been recently expanding into several disciplines. It is suitable for analyzing the properties of solids and its advantage consists in easy pretreatment of the investigated material. IGC allows the measurement of values of some complicated measurable characteristics of pharmaceutical materials, such as surface energy of powders, acid-base and polar properties of the surface [4]. These properties influence behaviour and technological processing of the materials.

This work is focused on the functional characteristics of lactose, which can be observed by differences in crystallinity of each batch manufactured by the same or a different technique, or even another manufacturer. The results can determine whether a transition to another form of lactose occurred, and how its properties are affected.

For characterization of lactose IGC method was used, through which it can be evaluated the surface properties of pharmaceutical powders. As a result, the effects of external environment can be examined. For example the influence of humidity on changes in surface properties and thus the structure and composition changes of the sample can be determined. One of the indicators of surface properties is the surface free energy. Its measurement by IGC compared with conventional methods is very simple, reproducible, and particularly non-destructive.

IGC is carried out in the infinite dilution, in which any adsorbed molecule is theoretically not in such proximity to other molecules adsorbed on surface, to allow their interaction [5]. The adsorbed molecules are basically isolated and the interaction cannot occur in the vapor phase, on the surface, or between desorbed and adsorbed molecules. There is a lack of interaction, which means that the parts of the sample with the highest surface energy are preferable to those with lower energy. Therefore, there is the assumption that IGC analyzes preferably sites of high energy and retrieves the value of dispersive surface

energy, which is representative [6]. Free surface energy (λ_s) of solids consists of a dispersive component (λ_S^D) and a specific component (λ_S^{SP}). The dispersive component describes London's interactions and the specific component other interactions, such as acid-base interactions or hydrogen bonds [7].

2. Experimentals

2.1. Materials

Three samples of lactose monohydrate – two different charges of Sorbolac (Meggle, Germany) and Pharmatose (DMV international, The Netherlands) and three samples of spray dried amorphous lactose from the same suppliers (two charges of DMV International and one Meggle) were used.

Solvents used as probes for IGC experiments (n-pentane, n-hexane, n-heptane, n-octane, diethyl ether, chloroform, acetone and benzene, all of them 99 %+) were supplied by Sigma Aldrich.

Lactose samples had to be dried overnight at 313 K prior to use. At this temperature the surface moisture is removed, but the water bound in the crystal structure remains in the sample. In the second part of this work the stability of lactose under conditions of 90 % relative humidity and 313 K was studied. The samples were dried at 313 K for one hour before the IGC measurements, and then were dried in-situ in the gas chromatograph to the constant response of a mass detector.

Measurement of the total specific surface area was performed on a commercial device Pulse Chemisorb 2700 Micromeritics that works on the principle of dynamic chromatographic methods. The total specific surface area was determined from the measured data of nitrogen physisorption at three different partial pressures in the area of the BET equation and at 77 K. Linearized form of the BET equation for the mathematical processing of measured data and to determine the total specific surface area was used.

2.2. Measurement of Surface Property with Inverse Gas Chromatography (IGC)

Experiments were performed using gas chromatograph with the mass detector (Shimadzu QP 2010). Samples of 200—500 mg of lactose were packed into a glass column of size of 5 mm o.d., 3 mm i.d. and 100 mm length, by vertical tapping until there were no visible cavities or channels in the body of the sample. Both ends of the column were loosely stoppered with silanised glass wool and attached to 5 m deactivated 0,1 mm i.d. capillary column. The conditioning of the column packed with the sample was carried out at 313 K, the experiment was performed at 303 K. Nitrogen was used as the inert probe; n-pentane, n-hexane, n-heptane and n-octane were used as non-polar probes; and chloroform, diethyl ether, acetone and benzene were employed as polar probes. All the probes were prepared by degassing with nitrogen and injected as gases into GC with gas tight microsyringe. The gas flow rate used was 2 ml/min and helium was used as the carrier gas. Each probe was injected 4 times to give a measure of the reproducibility. Powder surface energy can be calculated from the retention time of non-polar and polar probes. The methodology is described by Schultz et al [8]. As Kumon et al. reported [9] the basic relation employed is:

$$RT\ ln V_N = 2N(\lambda_S^D) \cdot A \cdot (\lambda_L^D) + C \qquad (1)$$

where R is the gas constant, T is the temperature (K), V_N is the net retention volume of the probe, N is Avogadro's number, A is the molecular surface area of the probe, λ_S^D is the dispersive component of the surface energy of the sample powder, λ_L^D is the dispersive component of the surface energy of the probe and C is a constant. Plotting $RT\ \ln V_N$ vs. $A \cdot (\lambda_L^D)^{1/2}$ for the non-polar probes yields a straight line (Fig.1).

The dispersive component of the solids is calculated from the slope in Eq. 1. The value of V_N was obtained from the retention times of the probes, and the value of A from measurement of the total specific surface area and values of λ_L^D were obtained from the literature [8] for polar probes and [10] for n-alkanes. The retention times for a homologous series of alkane probes and polar probes were used to calculate the acid-base parameters.

The retention behavior of polar probes on the $RT \ln V_N$ versus $A \cdot (\lambda_L^D)^{1/2}$ plot results in responses that are located above the line drawn through the alkane probe results, and the vertical distance between the data points of polar probes and the alkane line gives the specific energy of a polar probe adsorption for a solid material ΔG^{SP} [11]. The value of ΔG^{SP} is related to the acid or electron accepting parameter (K^A) and the base or electron donating parameter (K^B) and is calculated as in Eq. 2:

$$\Delta G^{SP} = RT \ln V_N - RT \ln V_N^{ref} \qquad (2)$$

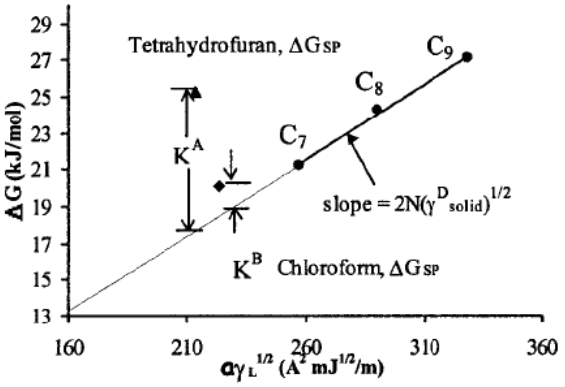

Fig. 1. Gibbs energy change for polar and nonpolar solvents [4]

3. Results and Discussion

3.1. Variation of surface properties for spray dried lactose and milled lactose monohydrate

Lactose samples labeled 1, 4 and 5 are spray dried, therefore they are amorphous and contain α- and β-anomers. Samples labeled 2, 3 and 6 are lactose monohydrate prepared by milling and sieving (200mesh), and contain lactose in crystalline and amorphous form.

Results given in Tab. 1 show that the values of the surface energy of lactose are dependent on the type of manufacturer. The values of the surface energy of lactose labeled 3 and labeled 6 supplied by Meggle are comparable. The value of spray-dried lactose labeled 1, supplied by the same company is higher, which corresponds to the assumption that the spray-dried lactose is amorphous. The amorphous form containing disordered molecules is thermodynamically unstable, and therefore in a higher energy state.

Table 1. Values of dispersive surface energy compared to different manufacturers and different treatment

Treatment	Manufacturer	Label	λ_S^D [mJm^{-2}]	ΔG^{SP} [mJmol^{-1}]		
				diethylether	chloroform	acetone
Spray dried lactose	Meggle	1	30.4	3.92	0.89	7.39
	DMV International	4	19.8	0.54	0.36	3.21
	DMV International	5	20.2	0.44	0.39	3.16
Milled and sieved lactose monohydrate (200 mesh)	DMV International	2	38.2	4.98	1.10	7.63
	Meggle	3	27.2	3.85	0.71	7.03
	Meggle	6	25.7	3.19	0.61	6.63

Spray-dried lactose produced by DMV has almost the same surface energy in the case of samples labeled 4 and 5. The value of the surface energy of lactose monohydrate from the same company is significantly higher. It is possible that the sample prepared by milling and sieving, containing crystalline and amorphous particles is more pronounced in the measured response of amorphous particles, as it is also mentioned by Ticehurst et al. [4] or Newell and Buckton [6]. During the milling treatment large defects may be created in the crystal structure of lactose and also many amorphous areas, which affect the surface properties of the studied material. Feeley et al. [12] show this phenomenon as the mechanical activation. It is probable that the effect of mechanical activation by the treatment of the sample labeled 2 by milling occurred.

Another factor responsible for the change of the surface energy can be the purity of studied material. The presence of impurities can significantly affect these values. By comparing samples of different batches of lactose from the same manufacturer, it can be found that they have similar values of the surface energy (lactose monohydrate Meggle), but compared to the different batches of spray dried samples (DMV International) the values are less reproducible. This difference may be caused by mechanical activation due to the milling of the material as described above or by the surface contamination or lactose, or a combination of both of the phenomena.

The highest difference between the values of ΔG^{SP} for polar solvents, which express the differences in specific interactions, was observed for samples labeled 4 or 5, which differs from the remaining samples of lactose in case of all used solvents. Specifically, the major differences between sample 4, respectively 5 and other batches of lactose are the values ΔG^{SP} for the base probe diethyl ether. The surface of lactose samples 4 and 5 has a less acidic behavior than others. The decrease in the change of Gibb‘s energy is also reflected by the reduction of the surface energy.

Higher values of the surface energy (λ_S^D) and ΔG^{SP} for samples labeled 1, 2, 3 and 6 suggest that a substantial portion of the surface of these lactose samples is located at a higher energy state for dispersive and for a specific component of surface free energy, so for non-polar and polar interactions.

3.2. Study of the influence of increased humidity and temperature on surface properties of lactose

Lactose monohydrate, formed by crystallization and subsequent milling and sieving contains the lactose in crystalline and amorphous form. Compared to spray drying lactose it should therefore be thermodynamically stable, with more regular arrangement of the surface. For most materials used in the pharmaceutical production, the crystallization takes place to the desired or optimal size of the crystals only in exceptional cases. The crystals are adjusted to the same level during the material processing. These adjustments may cause uncontrollable and variable range of defects or irregularities in the crystal structure [12]. The defects in the crystal structure caused by the mechanical activation [13] are only rarely

spread evenly across the surface, but most likely their occurrence prevails on the surface exposed to mechanical stress, which is the cause of disordered and amorphous areas on the particle surface [14]. Higher initial energy can be attributed to technological processing and mechanical activation. In Figure 2a is an obvious decreasing trend of surface energy on increasing the time delay in the exposure cell (313 K, 90% RH). Almost constant decrease is evidence of more regular arrangement of the surface of lactose and increased homogeneity in comparison with spray dried lactose. Decrease in surface energy may be caused by mutarotation of α-lactose to β- or by interaction with water molecules and subsequent stabilization of pyranose rings of amorphous parts of lactose, as well as the crystallization of initially amorphous parts.

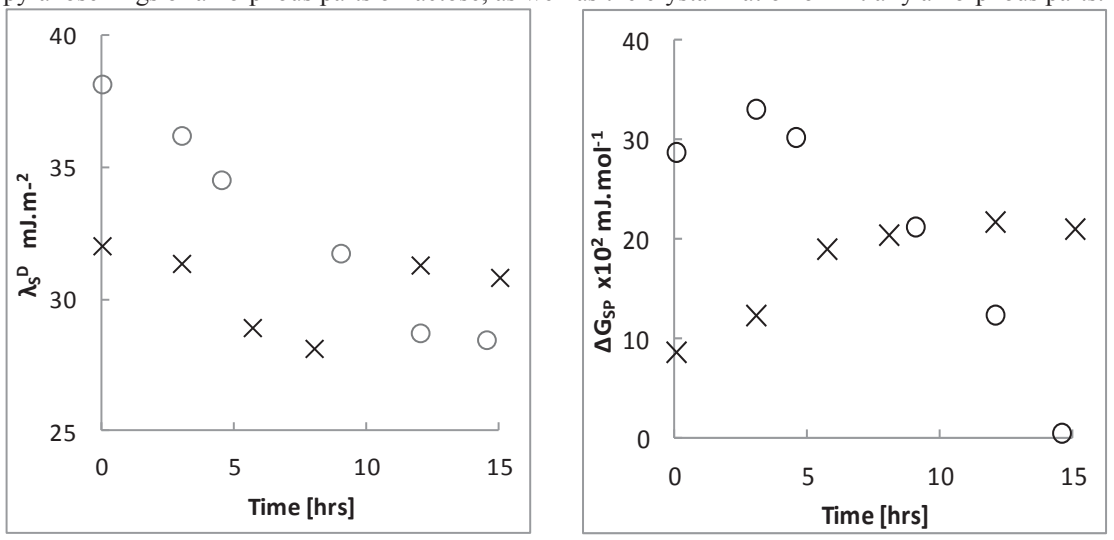

Fig. 2. a) Change of the dispersive surface energy in time b) Change of the specific surface interactions with diethyl ether in time; for 313 K and 90 % RH. (X – spray dried lactose, O – lactose monohydrate)

A dramatic decrease of the specific interactions of base ether probe with the surface of lactose monohydrate, depending on the time delay of lactose in exposure cell is shown in Fig. 2b. Decrease in the strength of the interactions between diethyl ether with the acidic centers on the surface of lactose is an indication of deterioration of the electron-acceptor properties of the surface and thus reducing the acidity of the surface. This may reflects a transformation or mutarotation of amorphous lactose formed during milling. On the contrary, an increase in specific interactions of the surface of amorphous spray dried lactose with molecules of base probe diethyl ether in the range of approx. $8–22 \cdot 10^{-2}$ mJmol^{-1} occurred. The surface of spray dried lactose appears to be more acidic respectively it seems to be more electron-accepting than at the beginning of these experiments.

A comparison of the two forms of lactose, although produced by one manufacturer but by various processes, shows that they are clearly different in chemical and physical properties as well. These were reflected in changes of acid-base interactions and the surface energy due to increased humidity.

4. Conclusions

The surface energy and the specific interactions were compared for each batch of lactose and effect of manufacturing method on these values was discussed. Significant differences occurred for the same type of lactose from different manufacturers. The second part of this work was focused on effect of the relative humidity and the temperature on the stability of lactose. The variations of the surface energy and the

specific interactions were studied over time for the conditions of 313 K and 90 % RH. The negative effect of higher temperature and air humidity leads to changes of the surface energy, deterioration of flow properties and mainly rapid change of electron-acceptor and electron-donor surface sites. It can cause serious problem in formulation with drug having strong acid or base character, where increasing or decreasing interactions with lactose can lead to changes of its efficiency.

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